REMARKS

Claims 1, 2, 24, and 28-44 are pending in the application. Claims 1, 2, 24, 29, 32, 34, 43, and 44 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claims 28, 30, 31, 33, 36, 37, and 39-42 are currently being examined on the merits. Applicants respectfully request clarification as to the status of claims 35 and 38, directed to methods of producing polyclonal and monoclonal antibodies with the specificity of the antibody of claim 28. These claims are listed as withdrawn on page one of the Office Action, however, on page 3 of the Office Action claims 35 and 38 are included both among the claims under consideration and among those withdrawn. Claims 35 and 38 are also included with the claims rejected under 35 U.S.C § 112, first paragraph, 35 U.S.C. § 102, and 35 U.S.C. § 103 (Office Action, pages 3, 5, 6, and 7). Applicants respectfully submit that these claims are indeed properly considered together with the claims to the antibodies produced by the recited methods (claims 37-38 and 39-40).

Applicants thank the Examiner for the acknowledgment that the rejoinder of the method claims will be considered upon determination of allowable product claims.

Claim 28 has been amended to incorporate the limitations of non-elected claim 1 and to further clarify the intended subject matter of the claimed invention. No new matter is added by this amendment. Entry of this amendment is respectfully requested.

Enablement rejections under 35 U.S.C. § 112, first paragraph:

Claims 28, 30-31, 33, and 35-42 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Office Action asserts that the specification, while enabling for an antibody which binds SEQ ID NO:2, or an immunogenic fragment of SEQ ID NO:2, does not provide enablement for an antibody which binds a naturally occurring amino acid sequence which is 90% identical to SEQ ID NO:2, or a polypeptide comprising a biologically active or immunogenic fragment of SEQ ID NO:2.

The Office Action asserts that the claims are overly broad since "insufficient guidance is provided as to which of the myriad of variant antigenic polypeptides encompassed by the claims will retain the characteristics of the GIPL polypeptide" (Office Action, pages 3-4). Applicants respectfully

point out that the claims are directed to antibodies, not to proteins; thus the function or "performance parameters" of the proteins to which the claimed antibodies bind is not relevant. What matters is that the recited variants are sufficiently similar to SEQ ID NO:2 so as to retain the same structure to which the specific antibodies bind. The Office Action further asserts that single amino acid changes in a protein's sequence can drastically affect the structure of the protein. In support of this assertion, the Office Action provides a single reference, Voet et al. Voet et al. teach that a single Glu to Val substitution in the subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (Office Action, page 4).

Applicants respectfully note that this example, relating to the hemoglobin/sickle-cell anemia gene sequences, is the exception, not the rule. In fact, Applicants assert that this is a case of the exception *proving* the rule. The sickle-cell example is a case in point: it is unusual in the extreme, and certainly should not be used to support the general argument that the Office Action is trying to make. The fact that the sickle-cell mutation has been perpetuated is due only to the fact that it confers an advantage (immunity to malaria) in heterozygous carriers. Generally, without such coincidence, the sickle-cell gene would have been selected against, because it causes a disease that disadvantages the carrier. Without this extraordinary twist of fate, the mutant gene would have been eliminated many generations ago. One can hardly expect this sort of serendipity to be a frequent occurrence. Note that the recited variants are naturally occurring, and hence have been subjected to natural selection which would eliminate structure altering mutations. In the present case, for the naturally occurring variants of GIPL, there is absolutely no reason to assume that there is any cause why such deleterious mutations would be selected for (and it is the Patent Office's burden in any case to show that this is more likely than not).

The Office Action provides no explanation for why the claimed antibodies which bind a polypeptide comprising a biologically active or immunogenic fragment of SEQ ID NO:2 are not enabled. Applicants note that claim 28, as amended herein to incorporate the limitations of non-elected claim 1, does not recite biologically active fragments of SEQ ID NO:2. The recited immunogenic fragments may also have biological activities, although they are not required to. Guidance to the

selection of immunogenic fragments is provided at, for example, page 46, lines 6-7, which disclose that appropriate epitopes include those near the C-terminus or in hydrophilic regions. A hydrophobicity plot for GIPL is provided in Figure 4 (see also the specification at page 5, lines 15-17).

Claim 28, as amended herein, recites antibodies which bind to "an immunogenic fragment of at least 10 contiguous amino acids of SEQ ID NO:2, wherein said polypeptide generates an antibody that specifically binds to SEQ ID NO:2." This phrasing clarifies that the specific antibody generated by the polypeptide comprising the immunogenic fragment of SEQ ID NO:2 binds specifically to SEQ ID NO:2, not to other unrelated portions of the comprising polypeptide. Thus the functions of these portions of the polypeptide need not be described as they do not pertain to the characteristics of the claimed antibodies. Applicants note that although these additional portions need not be described, potential such regions, such as domains that facilitate protein purification, are known in the art and described in the specification (see page 24, line 30 through page 25, line 6).

Written description rejections under 35 U.S.C. § 112, first paragraph:

Claims 28, 30-31, 33, and 35-42 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description. The Office Action asserts that "the scope of the claims includes numerous structural variants, and the genus is highly variant" and that ""[s]tructural features thta could distinguish compounds in the genus from others in the protein class are missing from the disclosure" (Office Action, page 5). Applicants respectfully point out that the claims are directed to antibodies, not proteins, and thus it is the properties of the antibodies, not the proteins they bind, which is relevant.

Applicants further note that claim 28, as amended herein, recites antibodies which bind to "an immunogenic fragment of at least 10 contiguous amino acids of SEQ ID NO:2, wherein said polypeptide generates an antibody that specifically binds to SEQ ID NO:2." Thus the genus of antibodies encompassed by claim 28(c) is not highly variant from that of claim 28(a), because the antibodies in both cases specifically bind to SEQ ID NO:2. Nor are the antibodies of claim 28(b) highly variant, given that they specifically bind to naturally occurring variants having at least 90% identity to SEQ ID NO:2. As discussed above, natural selection would tend to insure that the recited variants

retain the same structure as SEQ ID NO:2, so that the antibodies which specifically bound the recited variants would not be highly variant from those specifically binding to SEQ ID NO:2.

For this reason, it would be clear to one of skill in the art that the specification and claims do define the structural features of the recited polypeptides that are relevant to the antibodies which bind them. In the case of the polypeptides recited in claim 28(c), the structural feature is clearly the immunogenic fragment of SEQ ID NO:2, since it is this fragment that determines the antibody binding specificity. Given that SEQ ID NO:2 is clearly disclosed in the specification, one of skill in the art would not have difficulty in recognizing fragments of SEQ ID NO:2. Additional description of immunogenic fragments is provided at, for example, page 46, lines 6-7, which disclose that appropriate epitopes include those near the C-terminus or in hydrophilic regions, and the hydrophobicity plot shown in Figure 4. For the polypeptides recited in claim 28(b), the structural feature is the 90% amino acid sequence identity to SEQ ID NO:2. The fact that the recited variants are naturally occurring also in effect imposes a structural limitation, as these variants would have been selected by nature to retain the same overall structure as SEQ ID NO:2.

Furthermore, the recited polypeptide variants themselves do not describe a class which is highly variant. In support of this assertion, the Examiner's attention is respectfully directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40%

identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.

In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as GIPL proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:2. The "variant language" of the present claims recites, for example, antibodies which specifically bind to the polypeptides comprising "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:2" (note that SEQ ID NO:2 has 204 amino acid residues). This variation is far less than that of all potential GIPL proteins related to SEQ ID NO:2, i.e., those GIPL proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:2.

Rejections under 35 U.S.C. § 102:

Claims 28, 31, 33, and 35-42 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Baylink et al. Baylink et al. discloses antibodies which bind to peptides derived from human type 1 collagen. These peptides have six amino acids in common with SEQ ID NO:2, and the Office Action asserts that the antibodies generated against this peptide will specifically bind to SEQ ID NO:2.

Applicants respectfully point out that the Baylink patent defines "peptides" of procollagen α1 Type I to be "a contiguous chain of at least seven amino acids sequence residues from the procollagen α1 Type I N-terminal propeptide region" (Baylink, page 5, lines 28-31). Where Baylink describes peptides comprising only six amino acid residues, these residues are always selected from regions of procollagen that are not shared with SEQ ID NO:2 (see Baylink, page 7, lines 7-12, lines 17-22). Thus Baylink does not describe antibodies to the six amino acid sequence common to procollagen α1 Type I and SEQ ID NO:2.

Applicants also note that claim 28, as amended herein, recites antibodies to polypeptides comprising "an immunogenic fragment of at least 10 contiguous amino acids of SEQ ID NO:2, wherein said polypeptide generates an antibody that specifically binds to SEQ ID NO:2." The specification discloses that peptides used to induce antibodies specific to GIPL are preferably at least 10 amino acids in length, and mimic a portion of the amino acid sequence of the natural protein (specification,

page 11, lines 8-10). Thus the genus of polypeptides to which the recited antibodies specifically bind does not include any of the Baylink peptides, none of which comprise at least 10 contiguous amino acids of SEQ ID NO:2.

Applicants also respectfully submit that one of ordinary skill in the art would further understand that a specific antibody is one which distinguishes between the recited protein and other proteins. Specific antibodies are those useful, for example, in diagnostic assays to detect GIPL, not other unrelated proteins such as collagen (see the specification at, for example, page 28, lines 19-29). Clearly an antibody that binds to a six amino acid fragment shared by two such unrelated proteins as collagen and a phospholipase inhibitor (although not disclosed by Baylink) cannot be said to specifically bind to any protein.

For at least the above reasons, withdrawal of the rejection under 35 U.S.C. § 102 is respectfully requested.

Rejections under 35 U.S.C. § 103:

Claims 28, 30-31, 33, and 35-42 are rejected under 35 U.S.C. § 103 as allegedly being obvious over Baylink et al. in view of Queen et al. As discussed above, Baylink et al. does not disclose antibodies that specifically bind to SEQ ID NO:2, a naturally occurring variant having 90% identity to SEQ ID NO:2, or a polypeptide comprising at least 10 contiguous amino acids of SEQ ID NO:2. Queen et al. discloses humanized and single chain antibodies, but provides no disclosure of antibodies that bind the recited sequences; thus it fails to make up for the deficiencies of Baylink et al.

Withdrawal of the rejection under 35 U.S.C. § 103 is therefore respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: December 16, 2003

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Reference 1: Brenner, S.E. et al., "Assessing sequence comparison methods with reliably identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078.